MANAGEMENT OF ENDOCRINE DISEASE

Isolated maternal hypothyroxinemia during pregnancy: knowns and unknowns

Chrysoula Dosiou¹ and Marco Medici²¹Division of Endocrinology, Stanford University School of Medicine, Stanford, California, USA and²Department of Endocrinology and Rotterdam Thyroid Center, Erasmus Medical Center, Rotterdam, The Netherlands

Correspondence should be addressed to C Dosiou or M Medici

Emailcdosiou@stanford.edu or
m.medici@erasmusmc.nl

Abstract

Isolated maternal hypothyroxinemia (IMH) during pregnancy is defined as a low maternal T₄ in the absence of TSH elevation. As IMH is common, with a prevalence of 1–2% in iodine-sufficient populations, and early research has suggested adverse effects on fetal neurodevelopment, it has been the focus of many studies in the last decade. In the current review, we first discuss the significance of IMH based on data from animal models and recent discoveries regarding the role of thyroid hormone on neurodevelopment. We address issues surrounding the definition and prevalence of this entity and discuss new insights into the etiologies, clinical consequences and management of IMH. A number of large cohort studies have investigated the effects of IMH on the risk of various pregnancy complications and child neurodevelopment. We review these studies in detail and describe their limitations. We discuss the available research on management of IMH, including two recent randomized controlled trials (RCTs). Finally, we delineate the remaining uncertainties in this field and emphasize the need for a sufficiently powered, placebo-controlled RCT on the treatment of IMH early in the first trimester of pregnancy.

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Introduction

Thyroid hormone (TH) is critical for normal fetal development. The importance of TH in neurodevelopment is illustrated by conditions in which there is significant deprivation of neurons from this hormone. Severe iodine deficiency or mutations of the MCT8 thyroid hormone transporter in the brain are two such conditions that cause severe mental retardation. The significance of milder decreases of TH levels, however, remains unclear. Specifically, the entity of isolated maternal

hypothyroxinemia (IMH), which is the presence of low maternal T₄ in the absence of TSH elevation, has in recent years been the focus of increasing interest. Despite the fact that IMH is prevalent (1–2% of pregnant women in iodine-sufficient populations), and a number of studies in the last decade have shown associations with adverse neurodevelopmental outcomes, its causes as well as potential consequences have not yet been fully elucidated. The goal of this review is to summarize what is

Invited Author's profile

Marco Medici, MD, PhD, MSc, is a clinical endocrinologist at the Erasmus Medical Center in Rotterdam, the Netherlands. His principal areas of research include the effects of thyroid dysfunction during pregnancy. He is also the PI of an international consortium investigating the genetic determinants of the Hypothalamus–Pituitary–Thyroid axis.

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known regarding the epidemiology, causes, adverse effects and treatment of IMH, while also highlighting the areas of remaining uncertainty regarding this condition. We will first shortly review the changes in TH physiology in normal pregnancy, the role of TH in neurodevelopment and the various methods of T_4 measurement, as these topics are essential in the understanding of the remaining uncertainties in the field.

Background and significance

Thyroid physiology during pregnancy

The demands on the maternal thyroid significantly increase during pregnancy, through a number of mechanisms. Human chorionic gonadotropin (HCG) secreted by the placenta directly stimulates the TSH receptor, increasing TH production (1, 2). This results in a small transient increase in FT_4 with a reciprocal drop in TSH in the first trimester (1, 2). As thyroid-binding globulin synthesis increases 2.5-fold under the influence of estrogen (2), more TH production is needed to maintain adequate FT_4 levels. Thyroxine metabolism also increases, due to placental deiodinase activity, contributing to the need for increased TH production (2). Finally, there is increased renal clearance of iodine (3), which is a key element of TH. In order to meet the need for increased TH levels during pregnancy, the thyroid boosts its production by approximately 50%. In order for the maternal thyroid to successfully achieve this increase, it needs to have adequate iodine supply and also not suffer from significant underlying autoimmunity.

Thyroid hormone and fetal brain development

The main TH needed for fetal neurodevelopment is T_4 . T_4 enters the fetal brain, where it is converted by local deiodinases to T_3 , which then acts on local thyroid receptors to affect different aspects of neurodevelopment (4). Fetal thyroid function in humans starts at 18–22 weeks gestation (16–20 weeks after conception), so before that time, the fetus is exclusively dependent on maternal T_4 . Inadequate supply of maternal T_4 to the fetus before the onset of fetal thyroidal maturation can significantly influence processes that occur during that neurodevelopmental window, such as neuronal migration and proliferation. This concept is well supported by animal studies, as described below. It has been suggested that teleologically the HCG-mediated increase in T_4 production in the first trimester is an evolution of the

conceptus to ensure that it will be exposed to adequate FT_4 during its critical phase of neurogenesis (5).

During the last three decades, a number of important observations have supported the critical role of thyroid hormone in neurodevelopment. In 1984, Bernal and Pekonen first identified high-affinity nuclear TH receptors (TRs) in the human fetal brain as early as 8 weeks gestation (6). Subsequent studies in the next two decades identified T_4 in coelomic fluid at 6 weeks gestation (7) and further described the details of TRs and deiodinase activity in early fetal brain (8, 9, 10). In more recent years, multiple TH responsive genes have been identified (11, 12), including genes involved in differentiation, migration, myelination, axonal growth and synapse formation. Thyroid hormone is believed to play a key role in the processes of neuronal migration in the hippocampus and neocortex, development of cortical connections, cytoskeleton assembly, and neuronal development and maturation.

Animal models of IMH

Successful animal models of maternal hypothyroxinemia have been developed and have shown that even transient early IMH can cause structural and functional changes in developing brains, which can only be prevented with timely levothyroxine supplementation. Before discussing the relevant animal studies, it is useful to recognize some important differences between human and rat neurodevelopment. The development of the neocortex in humans occurs between the 6th and 24th week of gestation and the main waves of radial migration peak at 11 and 14 weeks gestation (reviewed in 12). In the rat, embryonic day 0 (E0) is the day of conception; birth occurs at E21–E22, while fetal thyroid is functional at E17.5–18. Neurogenesis and migration in the rat occur over 10 days, between E11 and E21, and therefore a period of 3 days in rat brain development corresponds roughly to 37–38 days in humans (13).

Animal studies designed to evaluate effects of IMH in neurodevelopment have used two models of inducing IMH: feeding dams iodine-deficient diets, or exposing dams to 3 days of methimazole causing mild thyroid hormone deficiency.

Lavado-Autric *et al.* studied cell migration and cytoarchitecture in the somatosensory cortex and hippocampus of 40-day-old progeny of dams fed low-iodine diet. Dams had normal serum T_3 but undetectable serum T_4 levels, with normal reproductive performance. Aberrant migration of cortical neurons was observed in

the 40-day-old offspring of mothers fed low-iodine diet; this was also seen in neurons that developed before the onset of fetal thyroid hormone secretion. There was also aberrant cytoarchitecture of the somatosensory cortex and hippocampus in the offspring, with blurred layering and abnormal barrel formation (14).

Ausó *et al.* (13) treated dams with 3 days of low-dose MMI early in gestation (E12–E15) and compared neurodevelopment and neurologic behavior in offspring of treated animals, controls or animals whose hypothyroidism was adequately treated with LT_4 for 3 days starting either 1 day after MMI (E13) or after 3 days (E15). IMH caused abnormalities in migration and cytoarchitecture of the somatosensory cortex and hippocampus. Treatment with T_4 could rescue this phenotype if done early (starting day E13) but not late (E15) (Fig. 1). Affected offspring showed abnormal behavior in response to acoustic stimuli with wild runs, followed in some with seizures, which could be prevented with early treatment with thyroid hormone (Fig. 1). This paper has important repercussions for human study design and timing of intervention, as neurogenesis in humans starts at E35–42 (gestational week 7–8), while the equivalent times to the above experimental timepoints would be human gestational week 7 for rat E11, week 10.5 for E13 and week 14 for E15 respectively. One could extrapolate that an intervention aimed to rescue neurodevelopmental repercussions of IMH in humans would be successful before gestational week 10.5 but not at gestational week 14.

In addition to the aberrant cytoarchitecture seen in the above studies, maternal hypothyroxinemia in animal models has been associated with a number of other structural changes, including limited dendritic growth of cerebellar Purkinje cells (15), delayed hippocampal axonal development (16) and alterations of glutamergic synapses (17). Functional consequences of maternal hypothyroxinemia in the fetus have been impaired spatial learning (17), impairment of long-term potentiation in the hippocampus (17) and increased frequency of abnormal response (wild runs or seizures) to audiogenic stimuli (13). Taken together, the available animal models clearly show detrimental effects of IMH on various aspects of fetal neurodevelopment.

Measurement of maternal T_4

Before defining IMH, it is important to review the caveats associated with T_4 measurement in pregnancy. Measurement of maternal T_4 is complicated by a number

Figure 1

Effects of early maternal hypothyroxinemia on fetal neurodevelopment. Adapted with permission from Ausó *et al.* (13). Pregnant rats were divided into four groups: one group of normal dams, one group that took only methimazole for 3 days (3dMMI₁₂), one that took methimazole with the addition of T_4 for 3 days, starting one day later, from E13–E16 (3dMMI₁₂ T_4 –13) and one group that took methimazole with additional T_4 starting 3 days later, from E15–E18 (3dMMI₁₂ T_4 –15). The onset of the day of treatment is indicated in the subscripts. A. Histograms show quantification of proliferating cells (immunoreactive to BrdU) in different cortical layers of the primary somatosensory cortex of pups born to the above treatment groups. Asterisks indicate a statistically significant difference between pups (normal and 3dMMI₁₂ T_4 –13 versus 3dMMI₁₂ T_4 –15 and 3dMMI₁₂). B. Responses of normal, 3dMMI₁₂, 3dMMI₁₂ T_4 –13, and 3dMMI₁₂ T_4 –15 pups to an acoustic stimulus. Bars reflect the proportion (median with 25th and 75th percentiles) of pups responding with wild runs followed by a seizure.

of factors. T_4 is mostly bound (99.97%): 60–75% bound to thyroid-binding globulin (TBG), 16–30% to transthyretin and 10% to albumin (18, 19). It is the very small free T_4 (FT₄) fraction (0.03%) that is responsible for T_4 actions and therefore the analyte most frequently used to assess TH levels in nonpregnant patients. In pregnancy, there are a number of changes in the thyroxine-binding proteins

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that affect results of FT₄ measurements. TBG levels increase 2.5-fold, albumin levels decrease and nonesterified fatty acid levels increase. These changes introduce inaccuracies in the FT₄ assessment, which can vary depending on the method.

FT₄ can be measured either through indirect methods such as immunoassays or through direct methods such as equilibrium dialysis or ultrafiltration that can be followed by liquid chromatography/tandem mass spectrometry. The FT₄ immunoassays significantly underestimate FT₄, while results vary greatly among the different assays. Sapin *et al.*, in a study using 9 different assays to measure FT₄ of 23 pregnant women in the 3rd trimester, showed the very poor correlation among the different assays, with the majority of the patients having low FT₄ levels when a nonpregnant reference range was used (20). Furthermore, FT₄ measured by immunoassays has been shown to not have the expected inverse correlation with TSH in pregnancy (21). Finally, FT₄ levels measured with immunoassays gradually fall as pregnancy progresses (21, 22).

In contrast to FT₄, the FT₄ index (typically calculated as total T₄ × thyroid hormone binding index) does have the expected small increase in the first trimester with subsequent decrease back to baseline and stabilization for the remainder of the pregnancy (22). It also exhibits the expected inverse relationship with TSH (22). However, this test is not widely available.

The direct methods of measuring FT₄ such as equilibrium dialysis (ED) and ultrafiltration followed by LC/MS/MS are designed to be free from interference from changes in binding proteins and free from cross-reactivity with heterophilic antibodies. These assays have shown better correlation with TSH than traditional immunoassays in nonpregnant patients (23), and show no correlation with albumin and TBG (24). However, there are important limitations in these methods as well. FT₄ measured through ultrafiltration followed by tandem mass spectrometry in pregnancy does not have a good inverse correlation with TSH (21). Ultrafiltration can result in loss of T₄ by adsorption to surfaces, while albumin separation depends on the membrane material used (25). ED takes a long time to perform (17–24 h) and has the disadvantages of the effects of the *in vitro* dilution of possible serum protein-binding inhibitors as well as interference from buffer ingredients (25). Furthermore, both ED and ultrafiltration methods require expensive equipment, and their availability is very limited.

Total T₄ (TT₄) is an alternative method of assessment of thyroxine levels. As shown in multiple studies from

around the world performed over the last few decades and summarized nicely by Lee *et al.* (22), TT₄ levels consistently increase to 150% of the nonpregnant values. Therefore, one could use the TT₄ measurement to assess thyroxine levels in pregnancy and multiply the nonpregnant reference range by 1.5 to get a pregnancy-specific reference range.

The 2011 American Thyroid Association guidelines recommend measuring FT₄ in the dialysate or ultrafiltrate of serum samples using online extraction/liquid chromatography/tandem mass spectrometry (26). If that is not available, they recommend using ‘whichever measure or estimate of FT₄ is available’, using method-specific and trimester-specific reference ranges (26). The 2012 Endocrine Society Guidelines regarding management of thyroid disease in pregnancy recommend using a trimester-specific range if measuring FT₄, or measuring TT₄ (with nonpregnant reference range multiplied by 1.5) or FT₄I (27) in order to assess thyroxine levels in pregnancy. The 2014 European Thyroid Association guidelines recommend establishing trimester-specific reference ranges for T₄ (total or free) (28). It is important for studies in this field to use one of these ways of assessing T₄ when defining IMH. Existing studies examining adverse outcomes of IMH have all used FT₄ assays to estimate thyroxine levels, as we review in a later section. One could therefore argue that the most informative assay clinically would be the FT₄ immunoassay, assuming that trimester-specific reference ranges are available.

Definition and prevalence of IMH

Unfortunately, consensus regarding the definition of IMH is lacking. In most studies, IMH is defined as an FT₄ below the 2.5th or 10th percentile with a normal TSH. The 2011 American Thyroid Association’s clinical guidelines on the management of thyroid disease in pregnancy defined IMH as a normal maternal TSH in conjunction with FT₄ in the lower 5th or 10th percentile of the reference range (26). However, there are substantial differences in the definition of IMH between studies, which significantly affect the interpretation of prevalence data for this condition. Different studies use different FT₄ percentile cutoffs, while there is no consistency in the assays used, and given the assay limitations described above, this creates disparate results. The reference ranges for FT₄ and TSH are not defined in a uniform way, as they are not always established in an iodine-sufficient and anti-thyroid

antibody negative pregnant population. The various studies use different gestational ages at the time of assessment, introducing added variability. Furthermore, ethnic variation as well as differential iodine status of the different populations further influences the T_4 laboratory values.

With those caveats in mind, the prevalence of IMH in the literature has ranged from 1.3 to 23.9%. Table 1 summarizes the prevalence data from different studies around the world, using different FT_4 cutoffs for their definition (Table 1). It is clear that the prevalence of IMH is higher, as expected, in countries with more severe iodine deficiency (36, 37). In addition, the prevalence is higher in studies that do not use pregnancy-specific reference ranges, as these do not account for the observed decrease in FT_4 seen with immunoassays in the pregnant state (34, 35).

Causes of IMH

The causes of IMH have not been completely delineated, but a number of new factors have been shown to be associated with this entity in recent years. The etiologies of IMH include iodine deficiency, environmental disruptors and novel causes such as obesity, iron deficiency and imbalance between pro- and anti-angiogenic factors (Table 2).

The most common cause of IMH is iodine deficiency. As reviewed above, during pregnancy, thyroid hormone production needs to increase by approximately 50%, while iodine clearance increases through higher glomerular filtration rate. When iodine becomes more scarce, the thyroid shifts its production of thyroid hormones from T_4 to T_3 , to conserve iodine. Vermiglio *et al.* in Italy have shown that pregnant women consuming a moderately iodine-deficient diet have higher T_3 and lower T_4 levels than women with adequate iodine in their diet (38). Consequently, the prevalence of IMH is higher in countries with iodine deficiency (Table 1). Even though significant progress has been made in efforts to eradicate iodine deficiency worldwide, this is still an important issue, as 2014 data show that greater than 50% of European countries have mild iodine deficiency (39), while in the most recent NHANES data (2007–2010), 26% of pregnant women in the US were found to have suboptimal iodine levels, with urinary iodine $<100\mu\text{g/L}$ (40). The implications of these findings are important, as iodine deficiency affects not only maternal but also fetal thyroid hormone production. Iodine deficiency during gestation has been linked to lower IQ in the offspring (41, 42), with prompt iodine supplementation resulting in improvement in IQ (37, 43). It is critical to educate women seeking pregnancy to take a prenatal multivitamin with $150\mu\text{g}$ iodine, to meet the goal of $250\mu\text{g}$ daily intake (26, 27).

Table 1 Prevalence of IMH.

Study	n	Country	Lower FT_4 cutoff (percentile)	Normal TSH range (mU/L) (how obtained)	Gestational week	Iodine status (at time of study)	Prevalence
(29)	17 298	USA	2.5%*	0.08–2.99 (PSRR)	6–20	Sufficient	1.3%
(30)	1099	USA	2.5%#	0.036–4.28 (ND) 0.213–3.93 (ND)	1st trim 2nd trim	Sufficient	2.1% 2.3%
(31)	1560	UK	2.5%*	0.09–3.03 (TSRR)	1st trim	No data	1.6%
(32)	4800	China	2.5%*	0.59–4.38 (GWSRR) 0.21–3.8 (GWSRR) 0.09–2.96 (GWSRR) 0.5–3.29 (GWSRR) 0.35–3.88 (GWSRR)	4 8 12 16 20	Sufficient	2.1%
(33)	6303	China	2.5%*	0.29–5.22 (TSRR)	4–8	Sufficient	2.4%
(34)	3659	Netherlands	5%** 10%**	0.03–2.5 (ES-G)	<18 weeks	Sufficient	4.3% 8.5%
(35)	514	Thailand	2.5%**	0.2–2.5 (OR)	≤14 weeks	Mildly deficient for pregnancy	8.4%
(36)	220	Italy	2.5%*	0.03–2.3 (TSRR) 0.29–2.8 (TSRR) 0.34–3.0 (TSRR)	1st trim 2nd trim 3rd trim	Deficient	3.2% 12.7% 9.5%
(37)	345	Spain	10%#	0.38–4.8 (ND)	1st trim 2nd trim 3rd trim	Deficient	23.9% 20.6% 26.5%

ND, not disclosed; ES-G, Endocrine Society Guidelines; GWSRR, gestational week-specific reference range; PSRR, pregnancy-specific reference range; TSRR, trimester-specific reference range; OR, outside reference.

* FT_4 range adjusted for gestational age; ** FT_4 range not adjusted for gestational age; #adjustment not reported.

Thyroid autoimmunity, well recognized as a risk factor for the development of thyroid dysfunction during pregnancy due to failure of the autoimmune thyroid to meet the increased thyroxine demands, does not seem to be an important etiologic factor with respect to IMH. In a longitudinal study of 220 pregnant women in Italy, only 7% of women with IMH were found to have thyroid autoimmunity (anti-TPO Abs), similar to the rate in the general pregnant population (8%) (36). In a larger study by Shan *et al.* of 4800 pregnant women in China, including 103 women with IMH, similar results were obtained, with 7–8% prevalence of thyroid autoimmunity in women with IMH, similar to nonpregnant controls (32).

Environmental contaminants are another factor that can cause selective T_4 decrease in pregnancy. There are many pathways of TH metabolism and action that are influenced by environmental pollutants; these are summarized in a comprehensive review by Pearce and Braverman (44). A number of studies have specifically investigated these relationships in pregnant women. Organochlorine pesticides activate hepatic uridine diphosphate glucuronyl transferase, causing increased glucuronidation of T_4 and subsequent drop in T_4 levels. Their levels have been associated with low serum T_4 in pregnancy (45, 46). Thiocyanate, a compound found in cigarette smoke, is a competitive sodium iodine symporter inhibitor, and FT_4 index levels have been shown to be lower in smokers than nonsmokers (47). Finally, polychlorinated biphenyls antagonize TH binding at the level of the thyroid receptor. Exposure to these agents is inversely associated with low T_4 levels in pregnancy (45).

Table 2 Causes of IMH.

Cause	Mechanism
Iodine deficiency	Preferential T_3 production to conserve iodine
Environmental pollutants	
Organochlorine pesticides	Activation of hepatic glucuronidation
Thiocyanate	Competitive inhibition of sodium iodine symporter
Polychlorinated biphenyls	Binding to the nuclear thyroid hormone receptor
Obesity	? Increased peripheral deiodination
Other	
Iron deficiency?	? Reduced activity of the heme-dependent thyroid peroxidase
Angiogenic factors?	? Antiangiogenic effects on thyroid

Obesity has also been recently associated with low FT_4 levels, through mechanisms that are incompletely understood (33, 35, 48, 49, 50). Mannisto *et al.* first reported an inverse association of FT_4 and body mass index (BMI) in iodine-sufficient anti-thyroid antibody negative pregnant women, while FT_3 was directly related to BMI (48). Pop *et al.* first showed in 2013 that BMI at 12 weeks of gestation was inversely correlated with FT_4 levels but not with TSH (49). Haddow *et al.* also showed that low FT_4 is associated with higher BMI in pregnant women, both in a reference population and in women treated for hypothyroidism (50, 51). Han *et al.* in a longitudinal study of Chinese pregnant women (iodine sufficient) at 4–8 weeks of gestation confirmed the inverse association of FT_4 with BMI in gestation and showed that the prevalence of IMH rises sharply when BMI increases above 24 kg/m^2 (33). One hypothesis regarding these findings, based on the increase in T_3 seen in association with the low T_4 , is that in obesity, there is increased peripheral deiodination (52), as leptin, produced by adipose tissue, is known to stimulate T_4 to T_3 conversion (53, 54). The effect of obesity on maternal T_4 levels is even more pronounced in iodine-deficient women, as shown in a recent study in Thailand, where mildly iodine-deficient overweight pregnant women had a 3.6-fold higher risk of developing low FT_4 than women of normal weight (35).

Finally, recent studies have suggested that iron deficiency and fetal angiogenic factors may play a role in the regulation of FT_4 levels. Iron deficiency is known to have multiple effects on the thyroid axis, and importantly affects TH synthesis by reducing the activity of the heme-dependent thyroid peroxidase (55). In the past, iron deficiency has been showed to be associated both with elevated TSH and with low FT_4 levels in pregnancy (56). Hu *et al.* have shown that iron deficiency without anemia in pregnant rats can also cause inhibition of thyroid peroxidase and decrease in TH levels, with the effect being more pronounced for T_4 than T_3 (57). A recent cross-sectional study of 3340 pregnant women in China, with sufficient iodine intake and no evidence of thyroid autoimmunity, showed that iron deficiency in the first trimester was associated with IMH (OR of 2.440 for mild IMH, defined as $FT_4 < 10\%$, and OR 3.278 for severe IMH, defined as $FT_4 < 5\%$) (58). These risks were similar to those conferred by increased BMI. Finally, a recent study from the Netherlands showed that increasing levels of either proangiogenic placental growth factor (PlGF) or antiangiogenic soluble FMS-like tyrosine kinase-1 (sFlt1; a vascular endothelial growth factor (VEGF) and PlGF antagonist), both important pregnancy-specific

angiogenesis regulators, are associated with increased risk of IMH (59). If these findings are replicated, future studies are needed to clarify the exact biological mechanisms behind these observed associations.

Effects on the risk of pregnancy complications

In the last two decades, a number of studies have investigated the effects of IMH on the risk of various pregnancy complications (29, 30, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70). While most of these studies were underpowered due to their limited sample size, a few large studies have been performed. Casey *et al.* determined serum TSH and FT₄ levels in 17 298 women presenting for prenatal care in the first 20 weeks of pregnancy, and identified 233 women with IMH, defined as a FT₄ level below the pregnancy-specific 2.5th percentile (P2.5), with a normal-range TSH (P2.5–97.5) (60). Compared with women with normal-range TSH and FT₄ levels, no differences in the risk of hypertensive disorders, diabetes, placental abruption and premature or cesarean deliveries were detected. In a similar approach, Cleary-Goldman *et al.* identified 232 and 247 women with IMH in the first and second trimesters of pregnancy, respectively, and studied their risk of a wide variety of pregnancy complications (30). While first-trimester IMH was associated with an increased risk of preterm labor and macrosomia, second-trimester IMH increased the risk of gestational diabetes, suggesting that the effects of IMH might be trimester-dependent. Although these endpoints are related and could therefore very well be the result of each other, the authors unfortunately did not perform conditional analyses. However, the results of this study need to be interpreted with caution, as a large number of tests were performed, which were not corrected for multiple testing. This is especially important, as for most of the tested associations, a clear *a priori* hypothesis based on pathophysiological mechanisms was lacking. In addition, many of the study endpoints were also rare, possibly leading to underpowered analyses. Interestingly, in a recent meta-analysis of Chan *et al.* including these and other smaller studies, the effects of IMH on the above-mentioned complications disappeared (68). Among the many endpoints studied, only the risk of placental abruption was found to be 2.3 times increased in mothers with IMH ($P=0.026$). The conflicting results of these studies on the effects of IMH can be partly explained by various sources of heterogeneity between

the individual studies. First of all, the definition of IMH was not consistent among studies, with FT₄ lower-range cutoffs ranging from the 2nd to a liberal 10th percentile (e.g., (2, 3, 4, 6)), while there were also differences in the definitions of the normal ranges for TSH and FT₄ levels (e.g., (60, 61, 62)). Furthermore, the timing of the diagnosis of IMH differed considerably, ranging from 10 to 13 weeks up until 20 weeks of pregnancy (30, 60, 62). As discussed above, this might be important, as the study by Cleary-Goldman *et al.* suggested trimester-specific effects of IMH (30). In addition, there are large differences between studies with respect to the level of detail in which endpoints have been investigated. This is exemplified by a study in a large Dutch pregnancy cohort, in which the effects of thyroid dysfunction during early pregnancy on the risk of premature delivery were investigated, showing that IMH was associated with an increased risk of premature delivery (64). While most studies are not able to differentiate between spontaneous and iatrogenic deliveries, a subanalysis was performed on spontaneous premature deliveries only, showing that the association between IMH and prematurity was driven by spontaneous and not iatrogenic deliveries. This might partly explain why smaller studies without detailed information on spontaneous or iatrogenic deliveries have not been able to show any effects of IMH on the risk of prematurity. Lastly, as mentioned, there are substantial differences in sample sizes between studies, with many studies working with only a limited number of cases leading to underpowered analyses, while not applying multiple-testing correction for the many tests performed (61, 62, 63, 69).

Taken together, while some of the currently available studies suggest significant, albeit small, effects of IMH on the risk of pregnancy complications, large detailed and sufficiently powered studies using consistent definitions for IMH and adverse pregnancy outcomes are needed to clarify the exact effects of IMH on pregnancy complications.

Effects on child neurodevelopment

While there are only a limited number of large well-conducted studies on the effects of IMH on pregnancy complications, far more studies have been performed on the effects on child neurodevelopment. This is driven by the many studies showing that overt hypothyroidism during pregnancy negatively affects child neurodevelopment (34, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86). Table 3 provides an overview of the studies on IMH

Table 3 Overview of studies on the effects of maternal hypothyroxinemia on offspring mental/motor development, and neuropsychiatric diseases.

Author (year) Country	Iodine insufficiency	No. of MH cases/controls	Lower FT ₄ percentile (pmol/L)	Normal-range TSH percentiles (U/L)	Gestational week	Study endpoints	Results
Pop et al. (2003) (80), The Netherlands	Sufficient	57/58 ^a	10th (12.4)	0.15–2.0 U/L ^b	12, 24, 32	Bayley mental and motor subscales at 12 and 24 months	IMH at 12, but not at 24 and 32 weeks associated with lower mental and motor scores at 12 and 24 months
Kooistra et al. (2006) (77), The Netherlands ^c	Sufficient	108/96 ^a	10th (12.4)	0.15–2.0 U/L ^b	12, 24, 32	Newborn development scores (NBAS) at 3 weeks	IMH at 12, but not at 24 and 32 weeks associated with worse orientation at 3 weeks. No effects on habituation, orientation, motor maturity, range and regulation of state, autonomic stability and reflexes
Henrichs et al. (2010) (34), The Netherlands	Sufficient	311 'mild IMH', 157 'severe IMH'/1775	10th (11.8; 'severe IMH'), 5th (11.0; 'mild IMH')	0.03–2.5 U/L ^d	13.3 (1.7) (mean (s.d.))	Expressive language delay at 18 (MCDI) and 30 months (LDS) and nonverbal cognitive delay at 30 months (PARCA)	'Mild' and 'severe' IMH associated with expres- sive language delay at 18 and 30 months (OR 1.4–1.8). 'Severe' but not 'mild' IMH associated with nonverbal cognitive delay at 30 months (OR 2.0)
Craig et al. (2012) (82), USA	Sufficient	99/99 ^e	3th (11.8)	0.1–3.5 U/L ^f	15–20	Mental and motor develop- ment scales (BSID-III) at 2 years	IMH not associated with mental and motor development at 2 years
Julvez et al. (2013) (83), Spain	Mild	82/1561 ^g	5th (8.4)	–	8–20 (median 13)	Bayley mental and psychomotor scales at 14 months	MH associated with lower mental, not psychomo- tor, scores at 14 months
Finken et al. (2013) (75), The Netherlands	Sufficient	175/1584 ^h	10th (7.7)	–	90 (83–100) (median (IQR)) days	Response speed (and stability), response selection/inhibition, and visuomotor skills scores (ANT) at 5–6 years.	MH associated with slower and decreased stability in response speed, not with response selection/ inhibition, and visuomo- tor skills, at 5–6 years
Ghassabian et al. (2014) (76), The Netherlands	Sufficient	129/3598	5th (11.0)	0.03–2.5 U/L ^d	13.5 (2.0) (mean (s.d.))	Nonverbal IQ test at 6 years (SONIT) and global brain volumetric measures, cortical thickness, and surface area using high-resolution structural MRI at 8 years (subset of 27 cases and 625 controls)	IMH associated with 4.3 points lower IQ at 6 years, no associations with brain morphology at 8 years.

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Päkkilä <i>et al.</i> (2015) (79), Finland	Sufficient	67/4746	2.5th (1st trimester: 11.4; 2nd trimester: 11.1)	P2.5–97.5 (1st trimester: 0.07–3.1 U/L; 2nd trimester: 0.10–3.5 U/L)	10.7 (2.8) (mean (s.d.))	School performance at 8 years (by main teacher), and self-reported performance at 16 years (Youth Self-Report subscales)	IMH associated with increased risk of boys, but not girls, repeating a school class (OR 5.46)
Neuro psychiatric diseases							
Modesto <i>et al.</i> (2015) (91), The Netherlands	Sufficient	127/3560	5th (10.9)	0.1–2.5 U/L ⁱ	13.6 (1.9) (mean (s.d.))	ADHD and oppositional symptoms (CPRS-R:S) at 8 years	IMH associated with more ADHD symptoms, but not with oppositional symptoms, at 8 years
Roman <i>et al.</i> (2013) (92), The Netherlands	Sufficient	295 'mild IMH', 136 'severe IMH'/3744	10th (11.8; 'mild IMH', 5th (11.0; 'severe IMH')	0.03–2.5 U/L ^d	13.4 (1.9) (mean (s.d.))	Behavioral and emotional symptoms at 6 years (PDP subscale of the CBCL1/2-5 and/or SRS)	'Severe' but not 'mild' IMH associated with higher risk of having a probable autistic child at 6 years (OR 3.9)
Gyllenberg <i>et al.</i> (2015) (98), Finland	Sufficient	185/1321	10th (14.0)	P5–95 (0.24–3.38)	10.9 (4.0) (mean (s.d.))	Risk of schizophrenia	IMH associated with schizophrenia (OR 1.8)

ADHD, attention deficit-hyperactivity disorder; ANT, Amsterdam Neuropsychological Tasks; BSID-III, Bayley Scales of Infant Development, third edition; CBCL, Child Behavior Checklist for Toddlers; CPRS-R:S, Connors' Parent Rating Scale-Revised Short Form; IQR, Interquartile range; LDS, Language Development Survey; MCDI, MacArthur Communicative Development Inventory; MH, Maternal hypothyroxinemia; MRI, magnetic resonance imaging; NBAS, Neonatal Behavioral Assessment Scale; PARCA, Parent's Report of Children's Abilities; PDP, Pervasive Development Problems; SONIT, Snijders-Oomen Nonverbal Intelligence Test; SRS, Social Responsiveness Scale.

^aControls defined as FT₄ P50–90 with TSH 0.15–2.0 U/L; ^bNo pregnancy-specific reference ranges used. Instead, a range for 20–40-year old women was applied (0.15–2.0 U/L); ^cExtension of the Pop *et al.* 2003 study; ^dRange based on the 2007 Endocrine Society Clinical Practice Guideline on management of thyroid dysfunction during pregnancy and postpartum. (Abalovich *et al.*, J Clin Endocrinol Metab 2007); ^eControls defined as FT₄ P10–90 with TSH 0.1–3.5 U/L; ^fManuscript does not state on which information this range was based; ^gCases defined as FT₄ < P5, irrespective of TSH level. Controls defined as having a FT₄ > P5, irrespective of TSH level; ^hCases defined as FT₄ < P10, irrespective of TSH level. Controls defined as FT₄ > P10, irrespective of TSH level; ⁱRange based on the 2011 American Thyroid Association guideline for the diagnosis and management of thyroid disease during pregnancy and postpartum. (Stagnaro-Green *et al.*, Thyroid 2011).

Review	C Dosiou and M Medici	Maternal hypothyroxinemia during pregnancy	176:1	R30
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and child neurodevelopment, stratified by study endpoint (mental/motor development or psychiatric diseases). Only studies with an arbitrary cutoff of at least 50 IMH cases were included, to exclude underpowered studies with a high risk of spurious results.

Mental development

It has already been more than 50 years ago that Man *et al.* conducted the first prospective clinical study on the effects of IMH on child neurodevelopment (71, 72, 73, 74). Among 1349 pregnant women, 36 were identified with maternal hypothyroxinemia, of which 15 received adequate thyroid hormone (TH) replacement therapy during pregnancy to correct the hypothyroxinemia. Children born to mothers with hypothyroxinemia and adequate TH replacement therapy had a similar development as children born to euthyroid mothers. However, children of inadequately treated mothers performed worse on various mental and motor scores at age 8 months, 4 and 7 years, including a lower mean IQ (at 7 years mean IQ 91.9 vs 104.5). Despite its small sample size, this study clearly illustrated the potential detrimental effects of low maternal thyroid function on the offspring. It surprisingly took the field more than 20 years before others started to study the effects of IMH on child neurodevelopment. In 2003, Pop *et al.* studied mental and motor development of 57 children born to mothers with IMH at 12 weeks gestation, defined as FT₄ level below the pregnancy-specific P10 with a normal-range TSH level (80). Their development at both 1 and 2 years of age was compared with 58 children born from mothers with normal-range TSH and high-normal FT₄ levels (P50–90). Children of mothers with IMH had worse mental and motor scores, with an average 8 and 10 points lower score on the Bayley mental and motor subscales. In an extension study of this cohort, including more cases and controls (Table 3), it was shown that in the children born from mothers with IMH, worse orientation scores could already be detected at 3 weeks of age (77). While very early neonatal behavior is rapidly evolving and difficult to assess, and the long-term predictive power of the used Neonatal Behavioral Assessment Scale remains questionable (78, 87), the results of the 2003 Pop *et al.* study showed that these children indeed continued to have worse neurodevelopmental scores at later timepoints. As cognition spans a broad range of subdomains, Henrichs *et al.* performed a study to gain more insight into the specific effects of IMH on cognitive functioning of the offspring (34). This study was performed in

3659 mother–child pairs from the Generation R study. Mild and severe IMH were defined as a pregnancy-specific FT₄ level below P10 and P5 respectively with a normal TSH level. Mild and severe IMH were associated with a 1.3–1.8 times increased risk of expressive language delay at age 18 and 30 months, while severe IMH was also associated with a two-fold increased risk of nonverbal cognitive delay at age 30 months. More recently, Finken *et al.* showed that IMH in early pregnancy is associated with a reduced performance on a simple reaction time test and a decreased stability in response speed in 5–6-year-old offspring, while performance on visuomotor performance tests was normal (75). These results point to a slower information processing speed.

The majority of the previously reviewed studies focused on the effects of IMH on mental development in early life. As some of these cohorts have continued follow-up of their participants over the years, they have also been able to study cognitive performance in later life. Ghassabian *et al.* investigated the effects of early pregnancy IMH ($n=129$), defined as a pregnancy-specific FT₄<P5 with a normal-range TSH, on child IQ levels at 6 years of age (76). These children's IQ was on average 4.3 points lower than the IQ of children born from euthyroid mothers. This was also the first study to investigate the associations between IMH and magnetic resonance imaging (MRI)-derived brain morphological data at 8 years of age, which was performed in a subset of 27 cases and 625 controls. Despite the effects on IQ levels, no differences in brain morphology were detected. This can be either due to the small sample size or because of the structural alterations resulting from IMH, which may not be global but rather involve specific brain subregions. However, the absence of effects is most likely explained by the fact that nonlinear associations were not investigated, it has been shown that there is an inverted U-shaped relation between maternal FT₄ and child IQ levels (84). This is supported by the fact that when data were reanalyzed using nonlinear models, associations of low FT₄ with lower gray matter and cortex volumes were found (84). Finally, the effects of early pregnancy IMH on school performance of 8- and 16-year-old offspring have recently been investigated in the Northern Finland Birth Cohort 1986 (79). This study showed that boys, but not girls, from mothers with IMH during pregnancy had a 5.5 times increased risk of repeating a school class. Such an effect has not been examined in any of the previous studies on IMH. As these gender-specific effects could still be a chance finding, these results first need replication in an independent cohort. If the findings are replicated,

the reasons behind the greater vulnerability of the male brains to IMH will need further investigation.

While the above studies clearly show that IMH is associated with worse cognitive performance, the study by Craig *et al.* did not find any effects of IMH on mental and motor scales at 2 years of age (Table 3) (82). This can be explained by the fact that this study investigated the effects of IMH diagnosed in gestational week 15–20, whereas the essential role of TH in brain development is predominantly restricted to the first trimester of pregnancy (4).

Motor development

Since overt maternal hypothyroidism increases the risk of not only mental but also motor neurodevelopmental delay (32), studies have also investigated whether IMH affects the motor development of the child (Table 3) (75, 77, 80, 82, 83). Indeed, most of these studies showed that IMH during early pregnancy is associated with an increased risk of a delay in motor development. The largest study was performed by Costeira *et al.* in a moderately iodine-deficient area in Portugal (81). Children born from mothers with an FT₄ below P25 had a 2.1-fold increased risk of mild-to-severe delay in psychomotor development. While these results are obviously not generalizable to iodine-sufficient areas, it is important to note that other studies from iodine-sufficient regions have also shown an increased risk of a delay in motor development in children born from mothers with IMH (80, 85, 86). As shown in Table 3, two studies did not find an effect of IMH on motor development of the child (82, 83). This can be partly explained by the fact that, in the study by Julvez *et al.*, the control group included all mothers with an FT₄ above the hypothyroxinemia FT₄ cutoff (83). This group therefore also included mothers with high FT₄ levels, and it has been shown that not only low but also high and even high-normal FT₄ levels can negatively affect child neurodevelopment (84). Furthermore, the authors tested the effects of low FT₄ levels, irrespective of the TSH status, and therefore tested a heterogeneous group that contained both purely hypothyroxinemic and overtly hypothyroid subjects. The negative findings in the study by Craig *et al.* (82) could be due to the fact that the effects of only second-trimester IMH were tested, beyond the timeframe when TH plays a crucial role in neurodevelopment (4). Taken together, these studies strongly suggest that IMH is associated with a delay not only in mental development but also in motor development, while more work is needed to clarify the exact effects on the various subdomains of

motor development, such as gross and fine motor skills, muscle control, body coordination and locomotion.

Neuropsychiatric diseases

In recent years, interest has shifted toward studying the effects of IMH on neuropsychiatric diseases. In 1993, Hauser *et al.* had already shown that individuals with a mutation in the TH receptor beta gene have an increased risk of attention-deficit hyperactivity disorder (ADHD) (89). A few years later, it was also shown that transgenic mice harboring a mutation in this receptor display ADHD-like symptoms, including hyperactivity and learning deficits (90). Recently, Modesto *et al.* studied the association between IMH and ADHD symptoms at age 8 years in 3873 mother–child pairs from the Generation R Study (91). Children born from mothers with IMH, defined as an FT₄ below the pregnancy-specific P5 with a normal-range TSH, had more ADHD symptoms, compared with children born from euthyroid mothers. These effects persisted after controlling for multiple confounders, including children's IQ. These mother–child pairs were also the subject of another study on autism (92), as transient gestational hypothyroxinemia in rodents has been shown to induce cortical neuronal migration brain lesions resembling those of autism (13, 14, 93, 94). When the children were 6 years of age, their parents completed questionnaires on behavioral and emotional symptoms. Children born from mothers with IMH showed more autistic symptoms compared with children from euthyroid mothers. Importantly, these effects were independent from the effects on ADHD symptoms. Besides, in these mother–child pairs, it has also been shown that IMH is associated with a larger fetal and infant head size (95), while it is known that children with autism spectrum disorders show increased head growth (96). Unfortunately, the authors did not correct the analyses on autism for head size, which could provide more insight into how these endpoints are related to one another.

Finally, schizophrenia is associated with disrupted prenatal neurodevelopment and impaired cognitive function (97), which is similar to the consequences of IMH. Gyllenberg *et al.* has studied the prevalence of IMH, defined as a pregnancy-specific FT₄ below P10 with a normal-range TSH, in 1010 case-control pairs from the Finnish Prenatal Study of Schizophrenia (98). IMH was associated with 1.8 times increased risk of schizophrenia, even after adjusting for confounders including maternal psychiatric history.

Review	C Dosiou and M Medici	Maternal hypothyroxinemia during pregnancy	176:1	R32
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Taken together, while the number of studies on the effects of IMH on neuropsychiatric endpoints are still limited and therefore need replication in independent cohorts, the currently available data strongly suggest that IMH should be seen as a risk factor not only for impaired mental and motor neurodevelopment but also for neuropsychiatric diseases of the offspring.

Prevention and treatment of maternal hypothyroxinemia

As the above studies have clearly shown an association between IMH in early pregnancy and child neurodevelopment, the key clinical question remaining is whether these complications can be prevented by timely correction of IMH. In the previously discussed studies by Man *et al.*, it was shown that the 15 children born to mothers with adequately treated IMH had a normal development, while the 21 children born to mothers with inadequately treated IMH had a worse mental and motor development (71, 72, 73, 74). However, this study is obviously limited by its small sample size, while the hypothyroxinemic group included mothers with not only IMH but also overt hypothyroidism. In the previously discussed Pop *et al.* study, a subgroup of 15 children, born from mothers with IMH at 12 weeks gestation but in whom FT₄ had increased at 24 and 32 weeks' gestation, had a similar development as the controls. While this observation is also based on only a limited number of subjects, and it is unclear when FT₄ started to normalize between 12 and 24 weeks gestation, these findings raise the question of whether, similar to the animal data described previously, correction of IMH in early pregnancy could potentially reverse the detrimental neurodevelopmental effects on the offspring. Two randomized controlled trials (RCTs) have studied the effects of levothyroxine treatment of women with IMH and (subclinical) hypothyroidism on child IQ. The Controlled Antenatal Thyroid Screening (CATS) study (99) randomized 21 846 women recruited in early pregnancy to testing of TSH and FT₄ levels during pregnancy versus serum sample storage and measurement after pregnancy. Women in the screening group with a TSH > P97.5, an FT₄ < P2.5, or both, were treated with a starting dose of 150 µg levothyroxine, with dose adjustments on subsequent thyroid function testing. An intention-to-treat analysis showed no difference in the children's IQ at 3 years, including mean IQ levels and percentage of children with IQ < 85 points, between the treated and nontreated group. A subanalysis restricted to

the mothers with IMH (FT₄ levels < P2.5 (N=411)) also did not show any significant differences. However, this study has a number of potential limitations. First, the study was not powered for the subgroup of mothers with IMH only. Second, one can question if an IQ test at 3 years is a reliable test for the detrimental effects of a shortage of TH on the fetal brain. For example, children born with congenital hypothyroidism who are treated promptly do not have a lower IQ, while they may have more subtle deficiencies in integrative and sensory functions (100). Third, the CATS study did not compare the IQ levels of the children born from mothers with thyroid dysfunction to children born from euthyroid mothers, and it therefore remains unclear if their screening strategy was effective at all in identifying a high-risk group. Finally, while brain development mainly takes place in the first trimester, treatment was started at a median gestational age of 13 weeks and 3 days. This may have been too late to restore any detrimental effects of TH shortage. The timing of levothyroxine intervention is a critical point, as animal models of IMH reviewed earlier, such as by Auso *et al.*, have shown that the neurodevelopmental effects on offspring born to hypothyroxinemic dams could only be rescued by TH replacement therapy in early pregnancy, but not with later intervention (13). Recently, also the first results of the Thyroid Therapy for Mild Thyroid Deficiency in Pregnancy study ('TSH study') were presented at the Society for Maternal-Fetal Medicine's Annual Meeting (101). For this RCT on the treatment of subclinical hypothyroidism and IMH, 97 226 pregnant women underwent TSH and FT₄ testing. Women with IMH (n=526), defined as an FT₄ < 0.86 ng/dL (11.1 pmol/L) with a normal-range TSH (0.08–3.99 U/L), were randomized to either levothyroxine or placebo at a mean gestational age of 17 weeks. Preliminary results showed no significant difference in offspring IQ at 5 years of age between the treated and untreated groups. Unfortunately, this study also has various limitations in common with the CATS study, including the fact that treatment was started at an even later timepoint in gestation. Furthermore, this study was designed to be powered to detect a 5-point difference in IQ at 5 years of age, while the study by Ghassabian *et al.* showed that IMH only leads to a 4.3 points lower IQ at 6 years of age (76). This suggests that this study would be underpowered to detect an effect of treatment of IMH with levothyroxine, even if this treatment would lead to a full restoration of a 4.3 point IQ loss. Over the years, various international guidelines on the treatment of thyroid dysfunction during pregnancy have provided recommendations on the treatment of IMH (26, 27, 28).

While the ATA guidelines published in 2011 recommended to not treat IMH, as solid evidence for a treatment benefit of IMH was still lacking (26), the 2011 Endocrine Society guidelines already left the choice of treatment to the discretion of the caregiver (27). The 2014 ETA guidelines also recommended to consider treatment of IMH, but importantly note that this should only be considered in the first trimester of pregnancy, when most harms of IMH on brain development are expected to take place (28). When considering treatment of IMH, one should also take the potential consequences of overtreatment into account, which inevitably takes place in a subset of treated patients. In this context, it is interesting to note that Korevaar *et al.* recently investigated the associations between early pregnancy thyroid function, child IQ at 6 years and brain MRI scans at 8 years of age (84). This study showed that not only low-normal early pregnancy FT₄ levels but also high-normal FT₄ levels are associated with decreased IQ levels of the offspring, as well as with smaller gray matter and cortex volumes. Although this study did not include mothers on TH replacement therapy, this study does suggest that treatment of IMH might carry the risk of adverse child neurodevelopment when the goal of treatment is to achieve high-normal FT₄ results. Given the above considerations, it is clear that a sufficiently powered RCT on the treatment of IMH early in the first trimester of pregnancy is still needed in order to answer the question of whether IMH should be treated or not.

A role for iodine supplementation

As discussed previously, iodine deficiency is still a global problem, affecting a subset of many European and United States' population. Restoring iodine status would be a relatively easy way to treat IMH in iodine-deficient women. In 2009, Berbel *et al.* studied the effects of iodine supplementation in early pregnancy in women with IMH from an iodine-deficient area in Spain (37). This study consisted of three groups: Group 1, children born from euthyroid mothers that started iodine supplementation at 4–6 weeks of gestation; Group 2, children born from mothers with early pregnancy IMH who started iodine supplementation at gestational weeks 10–12; and Group 3, children born from mothers with IMH at gestational weeks 37–40 who were treated with iodine supplementation after delivery and during lactation. Of the children born from mothers in group 2 and 3, 25.0 and 36.8% had neurodevelopmental delay at 18 months, while none of the children born from mothers in group

1 had neurodevelopmental delay. These results highlight the importance of optimizing iodine status in pregnant women as early in pregnancy as possible, preferably before conception, as has also been shown by others (37, 43). Optimizing iodine status of pregnant women asks for concerted actions by national authorities (102). On the individual level, the treating physician should, especially when dealing with pregnant women with IMH, get a sense of the iodine status of the patient by asking her dietary habits and intake of iodine-containing multivitamins. If needed, iodine supplementation should be started early, ideally a few months before conception, ensuring a daily intake of 250 µg/day (26, 27, 28, 102). Recently, Moleti *et al.* investigated the effects of iodine supplementation on child IQ in a prospective observational study in 60 mother–child pairs from an iodine-deficient region in Italy (103). Stratified for maternal histories of iodized salt consumption and levothyroxine treatment before and during pregnancy, the IQ test scores of the children at 6–12 years of age were compared. Irrespective of levothyroxine treatment, women consuming iodized salt for at least 2 years before pregnancy had children with better IQ scores compared with women not using iodine supplementation. Based on this, the authors suggested that neurodevelopmental outcome of children might be more dependent on maternal iodine status than on maternal thyroid function. Of note, this study was based on a limited sample size, with only 15 pairs per group, while many statistical tests were performed, resulting in a high risk of false-positive findings. Therefore, these results need to be interpreted with caution and first need replication in an independent, sufficiently powered study, ideally in a randomized controlled trial.

Finally, future studies should clarify whether also the iron status of these women should be determined, as one Chinese study showed that iron deficiency is associated with 2.4 times increased risk of IMH (58). Importantly, these effects were independent of iodine deficiency, and are supported by various studies showing that iron deficiency impairs TH synthesis and metabolism (55, 104, 105). However, as no other studies have investigated this association in pregnant women, replication in an independent study is warranted.

Remaining uncertainties

Although significant progress has been made in the last decade in the understanding of the detrimental effects of IMH during pregnancy, many uncertainties still surround this common disease, including its causes,

effects and treatment (Table 4). Currently, only iodine deficiency and several environmental pollutants are well-established causes of IMH. While obesity, abnormal levels of angiogenic factors and iron deficiency have all been associated with IMH, insight into the underlying pathogenetic mechanisms is still lacking. The fact that IMH is not associated with one but various risk factors could suggest that IMH is a heterogeneous group of diseases. A better understanding of its risk factors and underlying mechanisms is therefore not merely of academic interest; it is also essential to provide a basis for tailored management of IMH. Furthermore, the long-term effects of IMH have not been investigated, with existing studies focusing on the development of children in their first few years of life (Table 3). It is known that TH deficiency during critical early stages of neurodevelopment results in structural and functional changes in the brain (4, 13, 17), which are expected to cause irreversible neurological outcomes, with their severity depending on the degree of TH deficiency. IMH is therefore expected to have some impact on 'hard endpoints' later in life, such as academic achievement, socioeconomic status, quality of life and mortality. However, these effects still need to be characterized. Future studies on these endpoints should apply a consistent definition of IMH, using pregnancy- and population-specific reference ranges, while the exact FT₄ cutoff percentile for IMH still remains debatable, as studies have used a wide range of cutoff levels, with varying results (Table 3). Sensitivity analyses to pinpoint at what exact FT₄ level the detrimental effects start to occur will be informative. These studies should focus not only on child developmental outcomes, but also on the risk of pregnancy complications, as the currently available data on the latter risks remain inconclusive. Importantly, these studies should be carried out in well-documented cohorts with available

information on important potential confounders, such as socioeconomic status and parental educational levels.

While these studies will be important for developing a more precise definition of IMH and understanding of its clinical complications, the key clinical question, which still needs to be answered, is whether these complications can be prevented by timely correction of IMH. Ensuring a sufficient iodine status is essential, but it remains unclear if correction of IMH with TH replacement therapy is beneficial. As discussed, the two RCTs on treatment of maternal thyroid hypofunction in pregnancy were underpowered for IMH, while treatment started in the late first or early second trimester, when an important part of brain development has already taken place. It could therefore very well be that these studies missed the 'window of opportunity' of a successful intervention in the early first trimester, leading to negative results. We therefore call for a sufficiently powered, placebo-controlled RCT on the treatment of IMH with TH in the early first trimester. While there are insufficient data to recommend a specific gestational week when treatment should be started, it seems reasonable to aim for a treatment as early in the first trimester as possible, preferably before the sixth week of pregnancy (6, 7). If proven successful, treating pregnant women with IMH in early first trimester will be challenging, as most women do not present to antenatal care facilities before the second half of the first trimester. This will require concerted actions by national health authorities to increase public awareness of this condition and the need to present to antenatal care facilities as soon as pregnancy is confirmed. The road toward developing the optimal management of IMH is still challenging, but important to pursue given the condition's prevalence and potential complications.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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References

- Burrow GN, Fisher DA & Larsen PR. Maternal and fetal thyroid function. *New England Journal of Medicine* 1994 **331** 1072–1078. (doi:10.1056/NEJM199410203311608)
- Glinioer D. The regulation of thyroid function in pregnancy: pathways of endocrine adaptation from physiology to pathology. *Endocrine Reviews* 1997 **18** 404–433. (doi:10.1210/edrv.18.3.0300)

Table 4 Isolated maternal hypothyroxinemia: the knowns and unknowns.

Knowns
Common disease
Risk factors include iodine deficiency, environmental pollutants and obesity
Negatively affects child mental and motor development
Unknowns
Other risk factors and underlying pathophysiological mechanisms
Effects on pregnancy complications
Effects on mental and motor function in later life
Effects of treatment early in the first trimester

- 3 Glinoe D. Pregnancy and iodine. *Thyroid* 2001 **11** 471–481. (doi:10.1089/105072501300176426)
- 4 Williams GR. Neurodevelopmental and neurophysiological actions of thyroid hormone. *Journal of Neuroendocrinology* 2008 **20** 784–794. (doi:10.1111/j.1365-2826.2008.01733.x)
- 5 Morreale de Escobar G, Obregon MJ & Escobar del Rey F. Role of thyroid hormone during early brain development. *European Journal of Endocrinology* 2004 **151** (Supplement 3) U25–U37. (doi:10.1530/eje.0.151U025)
- 6 Bernal J & Pekonen F. Ontogenesis of the nuclear 3,5,3'-triiodothyronine receptor in the human fetal brain. *Endocrinology* 1984 **114** 677–679. (doi:10.1038/363458a0)
- 7 Contempré B, Jauniaux E, Calvo R, Jurkovic D, Campbell S & de Escobar GM. Detection of thyroid hormones in human embryonic cavities during the first trimester of pregnancy. *Journal of Clinical Endocrinology and Metabolism* 1993 **77** 1719–1722. (doi:10.1210/jc.77.6.1719)
- 8 Ferreira B, Bernal J, Goodyer CG & Branchard CL. Estimation of nuclear thyroid hormone receptor saturation in human fetal brain and lung during early gestation. *Journal of Clinical Endocrinology and Metabolism* 1988 **67** 853–856. (doi:10.1210/jcem-67-4-853)
- 9 Iskaros J, Pickard M, Evans I, Sinha A, Hardiman P & Ekins R. Thyroid hormone receptor gene expression in first trimester human fetal brain. *Journal of Clinical Endocrinology and Metabolism* 2000 **85** 2620–2623. (doi:10.1210/jcem.85.7.6766)
- 10 Kester MH, Martinez de Mena R, Obregon MJ, Marinkovic D, Howatson A, Visser TJ, Hume R & Morreale de Escobar G. Iodothyronine levels in the human developing brain: major regulatory roles of iodothyronine deiodinases in different areas. *Journal of Clinical Endocrinology and Metabolism* 2004 **89** 3117–3128. (doi:10.1210/jc.2003-031832)
- 11 Chatonnet F, Flamant F & Morte B. A temporary compendium of thyroid hormone target genes in brain. *Biochimica et Biophysica Acta* 2015 **1849** 122–129. (doi:10.1016/j.bbaggm.2014.05.023)
- 12 Berbel P, Navarro D & Román GC. An evo-devo approach to thyroid hormones in cerebral and cerebellar cortical development: etiological implications for autism. *Frontiers in Endocrinology* 2014 **5** 1–28. (doi:10.3389/fendo.2014.00146)
- 13 Ausó E, Lavado-Autric R, Cuevas E, Del Rey FE, Morreale de Escobar G & Berbel PA. Moderate and transient deficiency of maternal thyroid function at the beginning of fetal neocortico-genesis alters neuronal migration. *Endocrinology* 2004 **145** 4037–4047. (doi:10.1210/en.2004-0274)
- 14 Lavado-Autric R, Ausó E, García-Velasco JV, Arufe Mdel C, Escobar del Rey F, Berbel P & Morreale de Escobar G. Early maternal hypothyroxinemia alters histogenesis and cerebral cortex cytoarchitecture of the progeny. *Journal of Clinical Investigation* 2003 **111** 1073–1082. (doi:10.1172/JCI200316262)
- 15 Wang Y, Wang Y, Dong J, Wei W, Song B, Min H, Teng W & Chen J. Developmental hypothyroxinaemia and hypothyroidism limit dendritic growth of cerebellar Purkinje cells in rat offspring: involvement of microtubule-associated protein 2 (MAP2) and stathmin. *Neurobiology and Applied Neurobiology* 2014 **40** 398–415. (doi:10.1111/nan.12074)
- 16 Wei W, Wang Y, Wang Y, Dong J, Min H, Song B, Teng W, Xi Q & Chen J. Developmental hypothyroxinaemia induced by maternal mild iodine deficiency delays hippocampal axonal growth in the rat offspring. *Journal of Neuroendocrinology* 2013 **25** 852–862. (doi:10.1111/jne.12058)
- 17 Opazo MC, Gianini A, Pancetti F, Azkcona G, Alarcón L, Lizana R, Noches V, Gonzalez PA, Porto M, Mora S *et al.* Maternal hypothyroxinemia impairs spatial learning and synaptic nature and function in the offspring. *Endocrinology* 2008 **149** 5097–5106. (doi:10.1210/en.2008-0560)
- 18 Oppenheimer JH. Role of plasma proteins in the binding, distribution, and metabolism of the thyroid hormones. *New England Journal of Medicine* 1968 **278** 1153–1162. (doi:10.1056/NEJM196805232782107)
- 19 Hoffenberg R & Ramsden DB. The transport of thyroid hormones. *Clinical Science* 1983 **65** 337–342. (doi:10.1042/cs0650337)
- 20 Sapin R, D'Herbomez M & Schlienger JL. Free thyroxine measured with equilibrium dialysis and nine immunoassays decreases in late pregnancy. *Clinical Endocrinology* 2004 **50** 581–584.
- 21 Kahric-Janovic N, Soldin SJ, Soldin OP, West T, Gu J & Jonklaas J. Tandem mass spectrometry improves the accuracy of free thyroxine measurements during pregnancy. *Thyroid* 2007 **17** 303–311. (doi:10.1089/thy.2006.0303)
- 22 Lee RH, Spencer CA, Mestman JH, Miller EA, Petrovic I, Braverman LE & Goodwin TM. Free T4 immunoassays are flawed during pregnancy. *American Journal of Obstetrics and Gynecology* 2009 **200** 260.e1–260.e6. (doi:10.1016/j.ajog.2008.10.042)
- 23 Jonklaas J, Kahric-Janovic N, Soldin OP & Soldin SJ. Correlations of free thyroid hormones measured by tandem mass spectrometry and immunoassay with thyroid-stimulating hormone across 4 patient populations. *Clinical Chemistry* 2009 **55** 1380–1388. (doi:10.1373/clinchem.2008.118752)
- 24 van Deventer HE, Mendu DR, Remaley AT & Soldin SJ. Inverse log-linear relationship between thyroid-stimulating hormone and free thyroxine measured by direct analog immunoassay and tandem mass spectrometry. *Clinical Chemistry* 2011 **57** 122–127. (doi:10.1373/clinchem.2010.154088)
- 25 Holm SS, Hansen SH, Faber J & Staun-Olsen P. Reference methods for the measurement of free thyroid hormones in blood. Evaluation of potential reference methods for free thyroxine. *Clinical Biochemistry* 2004 **37** 85–93. (doi:10.1016/j.clinbiochem.2003.09.009)
- 26 Stagnaro-Green A, Abalovich M, Alexander E, Azizi F, Mestman J, Negro R, Nixon A, Pearce EN, Soldin OP, Sullivan S *et al.* American Thyroid Association Taskforce on Thyroid Disease During Pregnancy and Postpartum. Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. *Thyroid* 2011 **21** 1081–1125. (doi:10.1089/thy.2011.0087)
- 27 De Groot L, Abalovich M, Alexander EK, Amino N, Barbour L, Cobin RH, Eastman CJ, Lazarus JH, Luton D, Mandel SJ *et al.* Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society clinical practice guideline. *Journal of Clinical Endocrinology and Metabolism* 2012 **97** 2543–2565. (doi:10.1210/jc.2011-2803)
- 28 Lazarus J, Brown RS, Daumerie C, Hubalewska-Dydejczyk A, Negro R & Vaidya B. European thyroid association guidelines for the management of subclinical hypothyroidism in pregnancy and in children. *European Thyroid Journal* 2014 **3** 76–94. (doi:10.1159/000362597)
- 29 Casey BM, Dashe JS, Spong CY, McIntire DD, Leveno KJ & Cunningham GF. Perinatal significance of isolated maternal hypothyroxinemia identified in the first half of pregnancy. *Obstetrics & Gynecology* 2007 **109** 1129–1135. (doi:10.1097/01.aog.0000262054.03531.24)
- 30 Cleary-Goldman J, Malone FD, Lambert-Messerlian G, Sullivan L, Canick J & Porter TF. Maternal thyroid hypofunction and pregnancy outcome. *Obstetrics & Gynecology* 2008 **112** 85–92.
- 31 Vaidya B, Anthony S, Bilous M, Shields B, Drury J, Hutchison S & Bilous R. Detection of thyroid dysfunction in early pregnancy: universal screening or targeted high-risk case finding? *Journal of Clinical Endocrinology and Metabolism* 2007 **92** 203–207. (doi:10.1210/jc.2006-1748)
- 32 Shan ZY, Chen YY, Teng WP, Yu XH, Li CY, Zhou WW, Gao B, Zhou JR, Ding B, Ma Y *et al.* A study for maternal thyroid hormone deficiency during the first half of pregnancy in China. *European Journal of Clinical Investigation* 2009 **39** 37–42. (doi:10.1111/j.1365-2362.2008.02055.x)

Review	C Dosiou and M Medici	Maternal hypothyroxinemia during pregnancy	176:1	R36
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- 33 Han C, Li C, Mao J, Wang W, Xie X, Zhou W, Li C, Xu B, Bi L, Meng T *et al.* High body mass index is an indicator of maternal hypothyroidism, hypothyroxinemia, and thyroid-peroxidase antibody positivity during early pregnancy. *BioMed Research International* 2015 **2015** 351831. (doi:10.1155/2015/351831)
- 34 Henrichs J, Bongers-Schokking JJ, Schenk JJ, Ghassabian A, Schmidt HG, Visser TJ, Hooijkaas H, de Muinck Keizer-Schrama SM, Hofman A, Jaddoe VV *et al.* Maternal thyroid function during early pregnancy and cognitive functioning in early childhood: the generation R study. *Journal of Clinical Endocrinology and Metabolism* 2010 **95** 4227–4234. (doi:10.1210/jc.2010-0415)
- 35 Gowachirapant S, Melse-Boonstra A, Winichagoon P & Zimmermann MB. Overweight increases risk of first trimester hypothyroxinaemia in iodine-deficient pregnant women. *Maternal and Child Nutrition* 2014 **10** 61–71. (doi:10.1111/mcn.12040)
- 36 Moleti M, Lo Presti VP, Mattina F, Mancuso A, De Vivo A, Giorgianni G, Di Bella B, Trimarchi F & Vermiglio F. Gestational thyroid function abnormalities in conditions of mild iodine deficiency: early screening versus continuous monitoring of maternal thyroid status. *European Journal of Endocrinology* 2009 **160** 611–617. (doi:10.1530/EJE-08-0709)
- 37 Berbel P, Mestre JL, Santamaría A, Palazón I, Franco A, Graells M, González-Torga A & de Escobar GM. Delayed neurobehavioral development in children born to pregnant women with mild hypothyroxinemia during the first month of gestation: the importance of early iodine supplementation. *Thyroid* 2009 **19** 511–519. (doi:10.1089/thy.2008.0341)
- 38 Vermiglio F, Lo Presti VP, Scaffidi Argentina G, Finocchiaro MD, Gullo D, Squatrito S & Trimarchi F. Maternal hypothyroxinaemia during the first half of gestation in an iodine deficient area with endemic cretinism and related disorders. *Clinical Endocrinology* 1995 **42** 409–415. (doi:10.1111/j.1365-2265.1995.tb02650.x)
- 39 Zimmermann MB, Gizak M, Abbott K, Andersson M & Lazarus JH. Iodine deficiency in pregnant women in Europe. *Lancet Diabetes & Endocrinology* 2015 **3** 672–674. (doi:10.1016/s2213-8587(15)00263-6)
- 40 Caldwell KL, Pan Y, Mortensen ME, Makhmudov A, Merrill L & Moye J. Iodine status in pregnant women in the National Children's Study and in U.S. women (15–44 years), National Health and Nutrition Examination Survey 2005–2010. *Thyroid* 2013 **23** 927–937. (doi:10.1089/thy.2013.0012)
- 41 Bath SC, Steer CD, Golding J, Emmett P & Rayman MP. Effect of inadequate iodine status in UK pregnant women on cognitive outcomes in their children: results from the Avon Longitudinal Study of Parents and Children (ALSPAC). *Lancet* 2013 **382** 331–337. (doi:10.1016/S0140-6736(13)60436-5)
- 42 Hynes KL, Otahal P, Hay I & Burgess JR. Mild iodine deficiency during pregnancy is associated with reduced educational outcomes in the offspring: 9-year follow-up of the gestational iodine cohort. *Journal of Clinical Endocrinology and Metabolism* 2013 **98** 1954–1962. (doi:10.1210/jc.2012-4249)
- 43 Velasco I, Carreira M, Santiago P, Muela JA, Garcia-Fuentes E, Sanchez-Munoz B, Garriga MJ, Gonzalez-Fernandez MC, Rodriguez A, Caballero FF *et al.* Effect of iodine prophylaxis during pregnancy on neurocognitive development of children during the first two years of life. *Journal of Clinical Endocrinology and Metabolism* 2009 **94** 3234–3241. (doi:10.1210/jc.2008-2652)
- 44 Pearce EN & Braverman LE. Environmental pollutants and the thyroid. *Best Practice & Research. Clinical Endocrinology & Metabolism* 2009 **23** 801–813. (doi:10.1016/j.beem.2009.06.003)
- 45 Chevrier J, Eskenazi B, Holland N, Bradman A & Barr DB. Effects of exposure to polychlorinated biphenyls and organochlorine pesticides on thyroid function during pregnancy. *American Journal of Epidemiology* 2008 **168** 298–310. (doi:10.1016/j.jri.2012.10.006)
- 46 Lopez-Espinosa MJ, Vizcaino E, Murcia M, Llop S, Espada M, Seco V, Marco A, Rebagliato M, Grimalt JO & Ballester F. Association between thyroid hormone levels and 4,4'-DDE concentrations in pregnant women (Valencia, Spain). *Environmental Research* 2009 **109** 479–485. (doi:10.1016/j.envres.2009.02.003)
- 47 Pearce EN, Oken E, Gillman MW, Lee SL, Magnani B, Platek D & Braverman LE. Association of first-trimester thyroid function test values with thyroperoxidase antibody status, smoking, and multivitamin use. *Endocrine Practice* 2009 **13** 33–39. (doi:10.4158/ep.14.1.33)
- 48 Männistö T, Surcel HM, Ruokonen A, Vääräsmäki M, Pouta A, Bloigu A, Järvelin MR, Hartikainen AL & Suvanto E. Early pregnancy reference intervals of thyroid hormone concentrations in a thyroid antibody-negative pregnant population. *Thyroid* 2011 **21** 291–298. (doi:10.1089/thy.2010.0337)
- 49 Pop VJ, Biondi B, Wijnen HA, Kuppens SM & Lvaader H. Maternal thyroid parameters, body mass index and subsequent weight gain during pregnancy in healthy euthyroid women. *Clinical Endocrinology* 2013 **79** 577–583. (doi:10.1111/cen.12177)
- 50 Haddow JE, Craig WY, Palomaki GE, Neveux LM, Lambert-Messerlian G, Canick JA, Malone FD & D'Alton ME. Impact of adjusting for the reciprocal relationship between maternal weight and free thyroxine during early pregnancy. *Thyroid* 2013 **23** 225–230. (doi:10.1089/thy.2012.0440)
- 51 Haddow JE, Neveux LM, Palomaki GE, Lambert-Messerlian G, Malone FD & D'Alton ME. An inverse relationship between weight and free thyroxine during early gestation among women treated for hypothyroidism. *Thyroid* 2015 **25** 949–953. (doi:10.1089/thy.2015.0085)
- 52 Biondi B. Thyroid and obesity: an intriguing relationship. *Journal of Clinical Endocrinology and Metabolism* 2010 **95** 3614–3617. (doi:10.1210/jc.2010-1245)
- 53 Reinehr T. Obesity and thyroid function. *Molecular and Cellular Endocrinology* 2010 **316** 165–171. (doi:10.1016/j.mce.2009.06.005)
- 54 Zimmermann-Belsing T, Brabant G, Holst JJ & Feldt-Rasmussen U. Circulating leptin and thyroid dysfunction. *European Journal of Endocrinology* 2003 **149** 257–271. (doi:10.1530/eje.0.1490257)
- 55 Hess SY, Zimmermann MB, Arnold M, Langhans W & Hurrell RF. Iron deficiency anemia reduces thyroid peroxidase activity in rats. *Journal of Nutrition* 2002 **132** 1951–1955.
- 56 Zimmermann MB, Burgi H & Hurrell RF. Iron deficiency predicts poor maternal thyroid status during pregnancy. *Journal of Clinical Endocrinology and Metabolism* 2007 **92** 3436–3440. (doi:10.1210/jc.2007-1082)
- 57 Hu X, Teng X, Zheng H, Shan Z, Li J, Jin T, Xiong C, Zhang H, Fan C & Teng W. Iron deficiency without anemia causes maternal hypothyroxinemia in pregnant rats. *Nutrition Research* 2014 **34** 604–612. (doi:10.1016/j.nutres.2014.06.007)
- 58 Yu X, Shan Z, Li C, Mao J, Wang W, Xie X, Liu A, Teng X, Zhou W, Li C *et al.* Iron deficiency, an independent risk factor for isolated hypothyroxinemia in pregnant and nonpregnant women of childbearing age in China. *Journal of Clinical Endocrinology and Metabolism* 2015 **100** 1594–1601. (doi:10.1210/jc.2014-3887)
- 59 Korevaar TI, Steegers EA, de Rijke YB, Visser WE, Jaddoe VV, Visser TJ, Medici M & Peeters RP. Placental angiogenic factors are associated with maternal thyroid function and modify hCG-mediated FT4 stimulation. *Journal of Clinical Endocrinology and Metabolism* 2015 **100** E1328–E1334. (doi:10.1210/jc.2015-2553)
- 60 Casey BM, Dashe JS, Wells CE, McIntire DD, Byrd W, Leveno KJ & Cunningham FG. Subclinical hypothyroidism and pregnancy outcomes. *Obstetrics & Gynecology* 2005 **105** 239–245. (doi:10.1146/annurev.cellbio.24.110707.175418)
- 61 Hamm MP, Cherry NM, Martin JW, Bamforth F & Burstyn I. The impact of isolated maternal hypothyroxinemia on perinatal morbidity. *Journal of Obstetrics and Gynaecology Canada* 2009 **31** 1015–1021. (doi:10.1016/S1701-2163(16)34345-6)
- 62 Su PY, Huang K, Hao JH, Xu YQ, Yan SQ, Li T, Xu YH & Tao FB. Maternal thyroid function in the first twenty weeks of pregnancy and subsequent fetal and infant development: a prospective

- population-based cohort study in China. *Journal of Clinical Endocrinology and Metabolism* 2011 **96** 3234–3241. (doi:10.1210/jc.2011-0274)
- 63 Breathnach FM, Donnelly J, Cooley SM, Geary M & Malone FD. Subclinical hypothyroidism as a risk factor for placental abruption: evidence from a low-risk primigravid population. *Australian and New Zealand Journal of Obstetrics and Gynaecology* 2013 **53** 553–560. (doi:10.1111/ajo.12131)
- 64 Korevaar TI, Schalekamp-Timmermans S, de Rijke YB, Visser WE, Visser W, de Muinck Keizer-Schrama SM, Hofman A, Ross HA, Hooijkaas H, Tiemeier H *et al.* Hypothyroxinemia and TPO-antibody positivity are risk factors for premature delivery: the generation R study. *Journal of Clinical Endocrinology and Metabolism* 2013 **98** 4382–4390. (doi:10.1210/jc.2013-2855)
- 65 Pop VJ, Brouwers EP, Wijnen H, Oei G, Essed GG & Vader HL. Low concentrations of maternal thyroxine during early gestation: a risk factor of breech presentation? *BJOG* 2004 **111** 925–930. (doi:10.1111/j.1471-0528.2004.00213.x)
- 66 Männistö T, Väärämäki M, Pouta A, Hartikainen AL, Ruokonen A, Surcel HM, Bloigu A, Järvelin MR & Suvanto E. Thyroid dysfunction and autoantibodies during pregnancy as predictive factors of pregnancy complications and maternal morbidity in later life. *Journal of Clinical Endocrinology and Metabolism* 2010 **95** 1084–1094. (doi:10.1210/jc.2009-1904)
- 67 Sheehan PM, Nankervis A, Araujo Junior E & Da Silva Costa F. Maternal thyroid disease and preterm birth: systematic review and meta-analysis. *Journal of Clinical Endocrinology and Metabolism* 2015 **100** 4325–4331. (doi:10.1210/jc.2015-3074)
- 68 Chan S & Boelaert K. Optimal management of hypothyroidism, hypothyroxinaemia and euthyroid TPO antibody positivity preconception and in pregnancy. *Clinical Endocrinology* 2015 **82** 313–326. (doi:10.1111/cen.12605)
- 69 Saki F, Dabbaghmanesh MH, Ghaemi SZ, Forouhari S, Ranjbar Omrani G & Bakhshayeshkaram M. Thyroid function in pregnancy and its influences on maternal and fetal outcomes. *International Journal of Endocrinology and Metabolism* 2014 **12** e19378. (doi:10.5812/ijem.19378)
- 70 Medici M, Korevaar TI, Schalekamp-Timmermans S, Gaillard R, de Rijke YB, Visser WE, Visser W, de Muinck Keizer-Schrama SM, Hofman A, Hooijkaas H *et al.* Maternal early-pregnancy thyroid function is associated with subsequent hypertensive disorders of pregnancy: the generation R study. *Journal of Clinical Endocrinology and Metabolism* 2014 **99** E2591–E2598. (doi:10.1210/jc.2014-1505)
- 71 Man EB, Brown JF & Serunian SA. Maternal hypothyroxinemia: psychoneurological deficits of progeny. *Annals of Clinical and Laboratory Science* 1991 **21** 227–239.
- 72 Man EB & Jones WS. Thyroid function in human pregnancy. V. Incidence of maternal serum low butanol-extractable iodines and of normal gestational TBG and TBPA capacities; retardation of 8-month-old infants. *American Journal of Obstetrics and Gynecology* 1969 **104** 898–908. (doi:10.1016/0002-9378(69)90644-9)
- 73 Man EB, Jones WS, Holden RH & Mellits ED. Thyroid function in human pregnancy. 8. Retardation of progeny aged 7 years; relationships to maternal age and maternal thyroid function. *American Journal of Obstetrics and Gynecology* 1971 **111** 905–916. (doi:10.1016/0002-9378(71)90945-8)
- 74 Man EB & Serunian SA. Thyroid function in human pregnancy. IX. Development or retardation of 7-year-old progeny of hypothyroxinemic women. *American Journal of Obstetrics and Gynecology* 1976 **125** 949. (doi:10.1016/0002-9378(76)90494-4)
- 75 Finken MJ, van Eijdsden M, Loomans EM, Vrijkotte TG & Rotteveel J. Maternal hypothyroxinemia in early pregnancy predicts reduced performance in reaction time tests in 5- to 6-year-old offspring. *Journal of Clinical Endocrinology and Metabolism* 2013 **98** 1417–1426. (doi:10.1210/jc.2012-3389)
- 76 Ghassabian A, El Marroun H, Peeters RP, Jaddoe VW, Hofman A, Verhulst FC, Tiemeier H & White T. Downstream effects of maternal hypothyroxinemia in early pregnancy: nonverbal IQ and brain morphology in school-age children. *Journal of Clinical Endocrinology and Metabolism* 2014 **99** 2383–2390. (doi:10.1210/jc.2013-4281)
- 77 Kooistra L, Crawford S, van Baar AL, Brouwers EP & Pop VJ. Neonatal effects of maternal hypothyroxinemia during early pregnancy. *Pediatrics* 2006 **117** 161–167. (doi:10.1542/peds.2005-0227)
- 78 Ohgi S, Arisawa K, Takahashi T, Kusumoto T, Goto Y, Akiyama T & Saito H. Neonatal behavioral assessment scale as a predictor of later developmental disabilities of low birth-weight and/or premature infants. *Brain and Development* 2003 **25** 313–321. (doi:10.1016/S0387-7604(02)00233-4)
- 79 Pääkkilä E, Männistö T, Hartikainen AL, Ruokonen A, Surcel HM, Bloigu A, Väärämäki M, Järvelin MR, Moilanen I & Suvanto E. Maternal and child's thyroid function and child's intellect and scholastic performance. *Thyroid* 2015 **25** 1363–1374. (doi:10.1089/thy.2015.0197)
- 80 Pop VJ, Brouwers EP, Vader HL, Vulsma T, van Baar AL & de Vijlder JJ. Maternal hypothyroxinaemia during early pregnancy and subsequent child development: a 3-year follow-up study. *Clinical Endocrinology* 2003 **59** 282–288. (doi:10.1046/j.1365-2265.2003.01822.x)
- 81 Costeira MJ, Oliveira P, Santos NC, Ares S, Saenz-Rico B, de Escobar GM & Palha JA. Psychomotor development of children from an iodine-deficient region. *Journal of Pediatrics* 2011 **159** 447–453. (doi:10.1016/j.jpeds.2011.02.034)
- 82 Craig WY, Allan WC, Kloza EM, Pulkkinen AJ, Waisbren S, Spratt DI, Palomaki GE, Neveux LM & Haddow JE. Mid-gestational maternal free thyroxine concentration and offspring neurocognitive development at age two years. *Journal of Clinical Endocrinology and Metabolism* 2012 **97** E22–E28. (doi:10.1210/jc.2011-1772)
- 83 Julvez J, Alvarez-Pedrerol M, Rebagliato M, Murcia M, Forns J, Garcia-Esteban R, Lertxundi N, Espada M, Tardón A, Riaño Galán I *et al.* Thyroxine levels during pregnancy in healthy women and early child neurodevelopment. *Epidemiology* 2013 **24** 150–157. (doi:10.1097/EDE.0b013e318276ccd3)
- 84 Korevaar TI, Muetzel R, Medici M, Chaker L, Jaddoe VW, de Rijke YB, Steegers EA, Visser TJ, White T, Tiemeier H *et al.* Association of maternal thyroid function during early pregnancy with offspring IQ and brain morphology in childhood: a population-based prospective cohort study. *Lancet Diabetes & Endocrinology* 2016 **4** 35–43. (doi:10.1016/s2213-8587(15)00327-7)
- 85 Li Y, Shan Z, Teng W, Yu X, Li Y, Fan C, Teng X, Guo R, Wang H, Li J *et al.* Abnormalities of maternal thyroid function during pregnancy affect neuropsychological development of their children at 25–30 months. *Clinical Endocrinology* 2010 **72** 825–829. (doi:10.1111/j.1365-2265.2009.03743.x)
- 86 Pop VJ, Kuijpers JL, van Baar AL, Verkerk G, van Son MM, de Vijlder JJ, Vulsma T, Wiersinga WM, Drexhage HA & Vader HL. Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in infancy. *Clinical Endocrinology* 1999 **50** 149–151. (doi:10.1046/j.1365-2265.1999.00639.x)
- 87 Brazelton TB & Nugent KJ. *Neonatal Behavioral Assessment Scale*, vol 137, 3rd edn. London, UK: Mac Keith Press, 1995.
- 88 Connolly KJ, Pharoah PO & Hetzel BS. Fetal iodine deficiency and motor performance during childhood. *Lancet* 1979 **2** 1149–1151. (doi:10.1016/S0140-6736(79)92382-1)
- 89 Hauser P, Zametkin AJ, Martinez P, Vitiello B, Matochik JA, Mixson AJ & Weintraub BD. Attention deficit-hyperactivity disorder in people with generalized resistance to thyroid hormone. *New England Journal of Medicine* 1993 **28** 997–1001. (doi:10.1056/NEJM199304083281403)

Review	C Dosiou and M Medici	Maternal hypothyroxinemia during pregnancy	176:1	R38
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- 90 McDonald MP, Wong R, Goldstein G, Weintraub B, Cheng SY & Crawley JN. Hyperactivity and learning deficits in transgenic mice bearing a human mutant thyroid hormone beta1 receptor gene. *Learning & Memory* 1998 **5** 289–301.
- 91 Modesto T, Tiemeier H, Peeters RP, Jaddoe VW, Hofman A, Verhulst FC & Ghassabian A. Maternal mild thyroid hormone insufficiency in early pregnancy and attention-deficit/hyperactivity disorder symptoms in children. *JAMA Pediatrics* 2015 **169** 838–845. (doi:10.1001/jamapediatrics.2015.0498)
- 92 Román GC, Ghassabian A, Bongers-Schokking JJ, Jaddoe VW, Hofman A, de Rijke YB, Verhulst FC & Tiemeier H. Association of gestational maternal hypothyroxinemia and increased autism risk. *Annals of Neurology* 2013 **74** 733–742. (doi:10.1002/ana.23976)
- 93 Roman GC. Autism: transient in utero hypothyroxinemia related to maternal flavonoid ingestion during pregnancy and to other environmental antithyroid agents. *Journal of the Neurological Sciences* 2007 **262** 15–26. (doi:10.1016/j.jns.2007.06.023)
- 94 Wegiel J, Kuchna I, Nowicki K, Imaki H, Wegiel J, Marchi E, Ma SY, Chauhan A, Chauhan V, Bobrowicz TW *et al.* The neuropathology of autism: defects of neurogenesis and neuronal migration, and dysplastic changes. *Acta Neuropathologica* 2010 **119** 755–770. (doi:10.1007/s00401-010-0655-4)
- 95 van Mil NH, Steegers-Theunissen RP, Bongers-Schokking JJ, El Marroun H, Ghassabian A, Hofman A, Jaddoe VW, Visser TJ, Verhulst FC, de Rijke YB *et al.* Maternal hypothyroxinemia during pregnancy and growth of the fetal and infant head. *Reproductive Sciences* 2012 **19** 1315–1322. (doi:10.1177/1933719112450338)
- 96 Courchesne E, Carper R & Akshoomoff N. Evidence of brain overgrowth in the first year of life in autism. *JAMA* 2003 **290** 337–344. (doi:10.1001/jama.290.3.337)
- 97 Welham J, Isohanni M, Jones P & McGrath J. The antecedents of schizophrenia: a review of birth cohort studies. *Schizophrenia Bulletin* 2009 **35** 603–623. (doi:10.1093/schbul/sbn084)
- 98 Gyllenberg D, Sourander A, Surcel HM, Hinkka-Yli-Salomaki S, McKeague IW & Brown AS. Hypothyroxinemia during gestation and offspring schizophrenia in a national birth cohort. *Biological Psychiatry* 2016 **79** 962–970. (doi:10.1016/j.biopsych.2015.06.014)
- 99 Lazarus JH, Bestwick JP, Channon S, Paradise R, Maina A, Rees R, Chiusano E, John R, Guaraldo V, George LM *et al.* Antenatal thyroid screening and childhood cognitive function. *New England Journal of Medicine* 2012 **366** 493–501. (doi:10.1056/NEJMoa1106104)
- 100 Zoeller RT & Rovet J. Timing of thyroid hormone action in the developing brain: clinical observations and experimental findings. *Journal of Neuroendocrinology* 2004 **16** 809–818. (doi:10.1111/j.1365-2826.2004.01243.x)
- 101 Casey BM. Effect of treatment of maternal subclinical hypothyroidism or hypothyroxinemia on IQ in offspring. Abstract S2. *American Journal of Obstetrics & Gynecology* 2015 **214** S2. (doi:10.1016/j.ajog.2015.10.023)
- 102 World Health Organization, UNICEF & International Council for the Control of Iodine Deficiency Disorders. *Assessment of Iodine Deficiency Disorders and Monitoring Their Elimination*, 3rd edn. Geneva, Switzerland: WHO, 2007.
- 103 Moleti M, Trimarchi F, Tortorella G, Candia Longo A, Giorgianni G, Sturniolo G, Alibrandi A & Vermiglio F. Effects of maternal iodine nutrition and thyroid status on cognitive development in offspring: a pilot study. *Thyroid* 2016 **26** 296–305. (doi:10.1089/thy.2015.0336)
- 104 Beard JL, Borel MJ & Derr J. Impaired thermoregulation and thyroid function in iron-deficiency anemia. *American Journal of Clinical Nutrition* 1990 **52** 813–819.
- 105 Hess SY & Zimmermann MB. The effect of micronutrient deficiencies on iodine nutrition and thyroid metabolism. *International Journal for Vitamin and Nutrition Research* 2004 **74** 103–115. (doi:10.1024/0300-9831.74.2.103)

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